

Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry

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Attention-deficit/hyperactivity disorder is a highly heritable and prevalent neuropsychiatric disorder estimated to affect 6% of school-age children¹⁻³. Its clinical hallmarks are inattention, hyperactivity and impulsivity^{4,5}, which often respond substantially to treatment with methylphenidate or dextroamphetamine. Etiological theories suggest a deficit in corticostriatal circuits, particularly those components modulated by dopamine. We developed a new functional magnetic resonance imaging procedure (T2 relaxometry) to indirectly assess blood volume in the striatum (caudate and putamen) of boys 6–12 years of age in steady-state conditions. Boys with attention-deficit/hyperactivity disorder had higher T2 relaxation time measures in the putamen bilaterally than healthy control subjects. Relaxation times strongly correlated with the child's capacity to sit still and his accuracy in accomplishing a computerized attention task. Daily treatment with methylphenidate significantly changed the T2 relaxation times in the putamen of children with attention-deficit/hyperactivity disorder, although the magnitude and direction of the effect was strongly dependent on the child's unmedicated activity state. There was a similar but nonsignificant trend in the right caudate. T2 relaxation time measures in thalamus did not differ significantly between groups, and were not affected by methylphenidate. Attention-deficit/hyperactivity disorder symptoms may be closely tied to functional abnormalities in the putamen, which is mainly involved in the regulation of motor behavior.

We assessed six healthy control boys (10.2 ± 1.5 years old) and 11 boys with attention-deficit/hyperactivity disorder (ADHD) (9.3 ± 1.6 years old) in this study, which was approved by the McLean Hospital Institutional Review Board. The healthy control subjects were screened using structured diagnostic interview (K-SADS-E; schedule for affective disorder and schizophrenia for school-age children, epidemiological version⁶), were free of any major psychiatric disorder and had no more than three of nine possible symptoms of inattention or hyperactivity-impulsivity by criteria in the *Diagnostic and Statistical Manual IV*. We included children with ADHD if they met criteria for ADHD in a structured diagnostic interview, and had at least six of nine symptoms of inattention or hyperactivity-impulsivity. Children with ADHD participated in a triple-blind (parent, child and

rater), randomized, placebo-controlled study of the effects of methylphenidate (0, 0.5, 0.8 or 1.5 mg/kg in divided doses) on activity, attention and functional magnetic resonance imaging (fMRI). Children with ADHD received placebo or specific dose of methylphenidate continuously for 1 week and at the end of the week were tested for drug efficacy using objective measures of attention and activity, and fMRI within 1–3 hours of their afternoon dose. The time between dose and testing was held constant for each subject throughout the four treatment conditions. We evaluated activity and attention in unmedicated healthy control subjects using the same procedure used for children with ADHD, and fMRI followed in the same time frame. Here, we have compared the fMRI results of the unmedicated healthy control subjects and the ADHD subjects on either placebo or the highest dose of methylphenidate.

We used T2 relaxometry, a new fMRI procedure, to derive steady-state blood flow measures and to test for enduring medication effects, in specific regions of the brain (Fig. 1a, regions of interest). Although conventional blood-oxygenation-level-dependent (BOLD) fMRI is a valuable technique for determining dynamic brain activity changes between baseline and active conditions, so far it has failed to provide insight into possible resting or steady-state differences in regional perfusion between groups of subjects, or to delineate the effects of chronic drug treatment on basal brain function⁷. T2 relaxometry, like BOLD, hinges on the paramagnetic properties of deoxyhemoglobin⁸. However, the mismatch between blood flow and oxygen extraction that occurs as an acute reaction to increased neuronal activity in BOLD does not persist in steady-state conditions. Instead, regional blood flow is regulated to appropriately match perfusion with ongoing metabolic demand⁹, and the deoxyhemoglobin concentration becomes constant between regions in the steady state. Therefore, regions with greater continuous activity would be perfused at a greater rate, and these regions would receive, over time, a greater volume of blood and a greater number of deoxyhemoglobin molecules per volume of tissue¹⁰. Thus, there should be an increase in the paramagnetic properties of the region that would be detectable as a decreased T2 relaxation time.

Conventional T2-weighted images provide only a rough estimate of T2, useful for identifying areas of pathology with very different T2 properties, such as tumors¹¹. To calculate T2 relax-

Table 1 Spearman correlation between T2 relaxation time and motor behavior during CPT

Regions	Rest–Activity measures		Complexity measure spatial scaling
	temporal scaling	% time immobile	
Bilateral			
Caudate	–0.098	–0.159	0.064
Putamen	–0.752*	–0.73*	0.63 [†]
Thalamus	0.152	0.194	–0.235
Unilateral			
R caudate	–0.115	–0.115	0.196
L caudate	–0.199	–0.270	0.054
R putamen	–0.77*	–0.748*	0.618*
L putamen	–0.691 [†]	–0.634 [†]	0.534 [‡]
R thalamus	–0.361	0.087	0.029
L thalamus	0.306	0.270	–0.260

*, $P < 0.001$; [†], $P < 0.005$; [‡], $P < 0.05$. R, right; L, left.

ation time (T2-RT) with sufficient accuracy to be able to reliably perceive small differences (about 2%) in the T2 of gray matter associated with functional changes in blood volume, we used ‘echoplanar imaging’ to establish a signal intensity decay curve based on 32 sequential measures at different echo times. For each of the 32 images, there was a refocused spin echo.

We obtained very accurate laboratory-based measures of activity and attention by having the children complete a computerized vigilance test while an infrared motion analysis system captured and recorded movements¹². We used these findings to determine whether there were associations between regional measures of T2-RT and the capacity to inhibit motor activity to low levels while attending to a monotonous but demanding task.

As expected, boys with ADHD on placebo did not sit as still as healthy control subjects during the attention tests. They spent more time moving (temporal scaling: $F_{1,14} = 9.42$; $P = 0.008$) and had less-complex movement patterns (spatial scaling: $F_{1,14} = 9.68$; $P = 0.008$). On the continuous performance task (CPT), a measure of attention, children with ADHD were also somewhat less accurate (92.0%, ADHD, compared with 97.1%, control; $F_{1,14} = 2.94$; $P = 0.10$), and had a more-variable response latency ($F_{1,14} = 3.11$; $P < 0.10$), although these differences did not reach statistical significance in this limited sample.

Based on previous imaging studies^{11,13–15}, we expected to find differences between children with ADHD and healthy control subjects in the caudate and putamen. We also expected that T2-RT in these regions would change with methylphenidate. The thalamus was evaluated as a contrast region in which we did not expect to find group differences or drug effects. No significant difference emerged between ADHD children on placebo and healthy control subjects in bilateral T2-RT measures for thalamus ($F_{1,14} = 0.60$; $P > 0.4$), and differences fell short of significance for the caudate nucleus ($F_{1,14} = 2.40$; $P = 0.14$). Unilateral evaluation showed no significant differences in either left or right thalamus, and a trend-level difference in right caudate ($F_{1,14} = 2.80$; $P = 0.12$).

In contrast, ADHD children and control subjects differed considerably in bilateral putamen T2-RT measures (77.9 ± 1.1 milliseconds, ADHD, compared with 76.1 ± 1.1 milliseconds, control; $F_{1,14} = 9.40$; $P = 0.008$). On average, T2-RT was 3.1% higher in ADHD than control subjects in the left putamen ($F_{1,14} = 14.5$; $P = 0.002$; Fig 1b) and 1.6% higher in the right putamen ($F_{1,14} = 2.62$; $P = 0.13$).

For healthy control subjects and ADHD children on placebo,

there were substantial and significant correlations between motor activity and T2-RT for the putamen bilaterally, but not for caudate or thalamus (Table 1). Temporal scaling and average time spent immobile, two measures of activity–inactivity, correlated, with r_s values of -0.752 ($P < 0.001$) and -0.730 ($P < 0.001$), respectively, with T2-RT in the putamen. The complexity of the movement pattern also correlated with T2-RT in the putamen ($r_s = 0.630$; $P < 0.01$). Similarly, in unilateral analyses, all three motor activity measures correlated with T2 measures for both right and left putamen (Table 1).

There were also strong correlations between measures of CPT performance and T2-RT in the putamen bilaterally (Table 2). Accuracy on the CPT correlated with an r_s of -0.807 ($P < 0.0001$) in response latency correlated with an r_s of 0.652 ($P < 0.005$). These associations were present for both right and left putamen (Table 2 and Fig. 2a).

Methylphenidate produced salient effects on attention, increasing performance accuracy ($F_{1,10} = 5.98$; $P < 0.05$) and reducing response variability (s.d.) from 242 to 149 milliseconds ($F_{1,10} = 14.5$; $P < 0.005$). Methylphenidate also produced significant effects on activity, producing a 126% increase in time spent immobile ($F_{1,10} = 5.47$; $P < 0.05$), and increasing the complexity of the movement pattern ($F_{1,10} = 5.73$; $P < 0.05$). However, the effects of the drug on activity were very dependent on the subject’s unmedicated activity level. For example, spatial complexity increased 52.6% in the six children who were objectively hyperactive (at least 25% more active than normal control subjects) on placebo ($F_{1,5} = 13.16$; $P < 0.02$), but was unaffected (increase of less than 8%) in the five ADHD children who were not ($P < 0.6$).

T2-RT in both right and left putamen was significantly altered by ongoing treatment with methylphenidate ($F_{1,9} = 12.81$; $P = 0.006$; ANCOVA), although the response was strongly related to the subject’s unmedicated activity state (Drug \times temporal scaling covariate, $F_{1,9} = 11.09$ and $P = 0.008$; Fig. 2b). Methylphenidate effects on T2-RT correlated strongly with basal activity levels (right, $r_s = 0.836$ and $P < 0.002$; left, $r_s = 0.581$ and $P = 0.06$). The overall effect of methylphenidate was to cause T2-RT values to converge to a common mean, decreasing T2-RT in hyperactive subjects and increasing T2-RT in less-active subjects. There were also very similar effects with the 0.8-mg/kg dose of methylphenidate. Methylphenidate failed to exert significant effects on T2-RT in thalamus ($F_{1,9} = 0.13$; $P > 0.7$). There was a trend-level difference in the right caudate ($F_{1,9} = 3.85$; $P = 0.08$).

As a higher T2-RT corresponds to lower perfusion, our findings

Table 2 Spearman correlation between T2 relaxation time and CPT performance

Region	Accuracy	Response s.d.
Bilateral		
Caudate	–0.131	0.027
Putamen	–0.807*	0.652*
Thalamus	0.281	–0.135
Unilateral		
R caudate	–0.020	–0.048
L caudate	–0.357	0.087
R putamen	–0.734*	0.629*
L putamen	–0.708*	0.538 [†]
R thalamus	0.200	–0.072
L thalamus	0.366	–0.161

*, $P < 0.001$; [†], $P < 0.01$; [‡], $P < 0.10$. R, right; L, left.

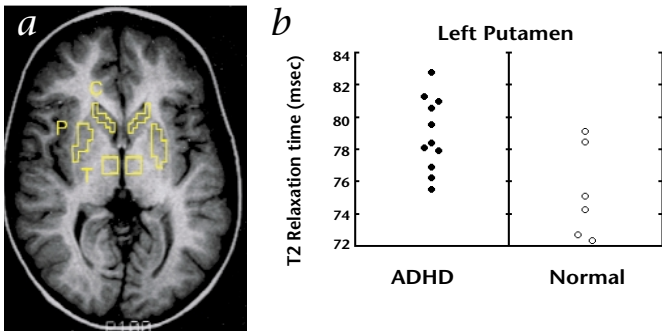


Fig. 1 Differences between ADHD and control subjects in T2-RT evaluated in specific regions of interest **a**, Yellow outlining indicates regions studied in caudate (C), putamen (P) and thalamus (T), drawn over a T1-weighted anatomical image of the basal ganglia and thalamus. These regions were used to ‘sample’ the T2 relaxation times. **b**, Scatter plots of individual T2 relaxation times for the left putamen of ADHD children treated with placebo (left) and healthy children (right). The increased T2 relaxation times in the ADHD sample indicate diminished regional blood volume.

of increased T2-RT measures in the putamen of children with ADHD and the correlation between T2-RT and objective markers of disease severity are consistent with some earlier studies. Abnormal or diminished blood flow was found in the corpus striatum of children with ADHD (refs. 13,14). Reduced glucose metabolism was found in right and left posterior putamen of adolescent females, but not males, with ADHD (ref. 15). Furthermore, our findings also indicate that a considerable proportion of the variance between subjects in degree of hyperactivity and inattention can be accounted for by T2-RT differences within the putamen alone.

Whereas the latter study¹⁵ found no significant reduction in glucose metabolism in caudate nuclei, the former two^{13,14} included only a single measurement of the caudate, putamen and associated internal capsule. By separating caudate from putamen, we, like the latter study¹⁵, found larger differences between patients with ADHD and control subjects in the putamen than the anterior caudate, and also found stronger associations between measures of activity and inattention with T2-RT measures in putamen. These findings may be due in part to the greater in-plane spatial resolution afforded by fMRI (3.125 mm for T2-RT compared with 5.2 mm for positron emission tomography¹⁶).

The basal ganglia seems to be organized into multiple parallel processing loops in which information is received from neocortex and projected back to frontal cortex. The sensorimotor inputs into the striatum are topographically organized and considerably expanded so that they occupy a volume 300–500% greater in the putamen than in the sensorimotor cortex¹⁷. The striatum seems to be organized to be essential in motor execution, including motor planning, sequencing, coordination and learning. Furthermore, the striatum serves as a ‘crossroads’ in which sensorimotor information can be combined with emotional information from the amygdala, and dopamine-mediated reward, reinforcement and arousal¹⁷.

Anatomical studies indicate that the putamen is most directly involved in regulation of motor activity and movement, whereas the anterior caudate subserves higher cognitive functions¹⁷. Thus, it is not unexpected that there is a more direct relationship between motor activity and T2-RT in the putamen than the anterior caudate. Also, the CPT task we used is particularly elementary, does not require holding information in working memory,

and mostly involves suppression of motor response to non-targets, fixation of gaze onto the computer screen and rapid response to visualized targets. Given the nature of the CPT task we used, it seems reasonable that we found a greater association between CPT performance and fMRI measures in the putamen than in the caudate nucleus.

Methylphenidate exerted different effects on T2 relaxometry of the putamen, presumably increasing perfusion in the more hyperactive children but decreasing perfusion in ADHD children with normal activity. Different response to methylphenidate is consistent with the observation that methylphenidate produces different BOLD fMRI effects in ADHD children than in healthy control subjects¹⁸. Also, a study of healthy adult males found that methylphenidate increases frontotemporal metabolism in subjects with high availability of dopamine D2 receptors and decreased metabolism in subjects with low availability of D2 receptors¹⁹. Behaviorally, our findings indicate that methylphenidate substantially attenuated the activity of ADHD subjects who are objectively hyperactive, but exerted little effect on ADHD children who were not objectively hyperactive. Thus, methylphenidate can exert rate-dependent effects that may vary in conjunction with the density of neuronal and vascular dopamine receptors.

These studies provide further evidence for the involvement of the striatum in that pathophysiology of ADHD, and indicate that there may be a direct neuroanatomical link between the capacity to inhibit motor activity and the capacity to sustain attention. Also, our results demonstrate that T2-RT may be a valuable new technique for the steady-state assessment of brain function and drug effects.

Methods

Assessment of activity and attention. Activity and attention data were obtained as described¹². Children sat in front of a computer and were evaluated using a simple ‘go/no-go’ CPT (refs. 12,20), in which the subject responds to visual presentation of a target and withholds response to non-target stimuli that appear in the center of the screen at a fixed, 2-second, inter-trial interval. The stimuli are simple geometric shapes that can be distinguished without right/left discrimination, and are designed to allow children with dyslexia to function as well as normal control subjects²⁰. Three 5-minute test sessions were recorded during a 30-minute test period while

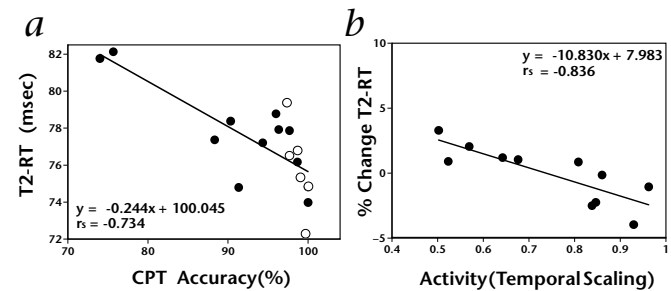


Fig. 2 Association between T2-RT and attention and influence of basal activity on T2-RT drug response. **a**, The association between T2-RT in right putamen and accuracy on the performance of the computerized attention task for children with ADHD on placebo (filled circles) and normal control subjects (open circles). There is a substantial inverse linear correlation between accuracy and T2 relaxation time (higher levels of T2-RT indicate lower perfusion). **b**, Percent change in T2-RT in the right putamen after treatment with methylphenidate in children with ADHD. The degree of response is affected by the baseline level of activity: the higher the temporal scaling, the greater the activity of the subject. Values below zero for change in T2-RT indicate enhanced regional blood volume after methylphenidate administration.

an infrared motion analysis system (Qualisys, Glastonbury, Connecticut) recorded the movement of small reflective markers attached to the head, shoulder, elbow and back of the child. The motion analysis system stored the precise vertical and horizontal position of the center of each marker 50 times per second to a resolution of 0.04 mm.

Results were analyzed using the idea of 'micro-events'. A new 'micro-event' begins when the marker moves 1.0 mm or more from its most recent resting location, and is defined by its position and duration. The spatial scaling exponent is a measure of the spatial complexity of the movement path, and is calculated from the logarithmic rate of information decay at progressively lower levels of resolution. The temporal scaling exponent is a scale invariant stochastic measure of percent time active. Values range from 0 (immobility) to 1 (incessant activity), and is calculated from the slope of the log-log relationship between the duration of micro-events and their frequency²¹. Software for presenting stimuli, recording activity and analyzing results was written by M.H.T., and is licensed to Cygnex (jtaylor@cygnex.com).

T2 relaxometry fMRI procedure and relaxation time computations.

Children were positioned in the scanner and were instructed to remain as still as possible. Images were acquired using a 1.5-T magnetic resonance scanner (Signa; General Electric Medical Systems, Milwaukee, Wisconsin) equipped with a whole-body, resonant-gradient set capable of echo planar imaging (Advanced NMR Systems, Wilmington, Massachusetts), and a standard 'quadrature' head coil for image detection. During each examination, three categories of images were obtained: 'scout' images (typically T1-weighted sagittal images); high-resolution, T1-weighted, matched axial images through the ten planes for which maps of T2 were generated; and 32 spin echo, echoplanar image sets, with the time to echo (TE) increased by 4 ms in each consecutive image set (for example, TE₁ = 32 ms, TE₂ = 36 ms, ..., TE₃₂ = 160 ms) through the same ten axial planes (time of repetition (TR)₃₂ = 10 s; slice thickness, 7 mm with a 3-mm skip; in-plane resolution, 3.125 mm × 3.125 mm; field of view, 200 mm). The 32 TE-'stepped' images were then transferred to an off-line workstation and corrected for in plane motion using a modification of the decoupled automated rotational and translational image registration algorithm²². The value of T2-RT was then estimated on a pixel-wise basis by linear regression of the signal intensity $S(x,y,n)$ assuming an exponential decay of $S(x,y,n)$ with time constant T2-RT(x,y), such that $\ln S(x,y,TE(n)) = \ln S(x,y,TE=0) - (TE(n)/T2-RT(x,y))$, where (x,y) is the pixel position and TE(n) is the spin-echo time corresponding to the nth image of the series.

Calculations of regional T2-RT were made for left and right anterior caudate, putamen and thalamus (as a contrast region) using anatomic boundaries observed in T1-weighted images and conservatively circumscribed to avoid encroaching into ventricular space (Fig. 1a, regions of interest). Delineation of regions and analysis of imaging data was made on coded images, and the responsible researcher was 'blinded' to the identity, diagnosis and treatment condition of the subject. T2-RT was calculated from the median value of all the designated pixels, as the median provides a regional estimate less susceptible to contamination by spurious values from bordering white matter and cerebrospinal fluid regions than the mean.

The intrinsic reliability of the T2-RT measure was determined using a within-subject procedure, with head repositioning as needed. There was a lag of about 5 min between end of the first session and start of the second session. Based on eight within-session comparisons with normal adult volunteers, there was a correlation of $r_s = 0.942$, and an average mean value difference of -0.17% for T2-RT of the putamen.

Statistical analyses. Differences between groups was assessed using ANCOVA, with age as a covariate. Although the groups did not differ significantly in age, the behavioral and fMRI measures showed age-dependent changes, and ANCOVA minimized this component of the error variance. Correlations were calculated using Spearman rank order test. Differences between behavioral and fMRI measures of ADHD subjects on

methylphenidate or placebo were assessed using repeated measure ANCOVA with placebo activity (temporal scaling) as a covariate. This was essential for the analysis, as methylphenidate effects are very rate-dependent, and basal activity on placebo accounted for about 50% of the magnitude of the medication effect.

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